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DICLOFENAC SUBMICRON PARTICLE CAPSULES DEMONSTRATE EARLY AND SUSTAINED ACUTE PAIN RELIEF IN A PHASE 3 STUDY IN PATIENTS FOLLOWING BUNIONECTOMY SURGERY

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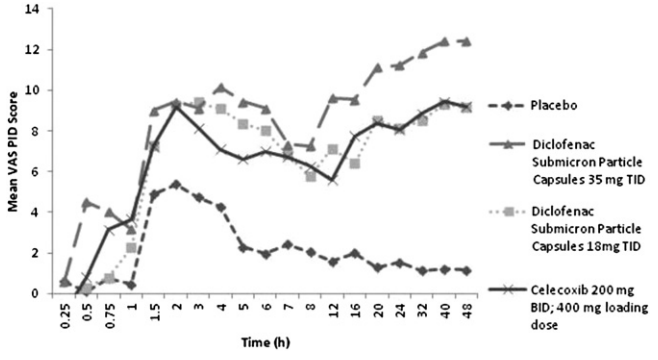
Purpose: Early management of acute pain may impact the severity and duration of pain. NSAIDs are utilized to treat acute pain but have the potential for serious dose-related gastrointestinal, cardiovascular, and renal adverse events (AEs). Investigational submicron particle NSAIDs using proprietary SoluMatrix™ technology are being evaluated to assess the potential to provide effective pain relief at lower doses than currently available oral NSAIDs. In a Phase 1 study, diclofenac submicron particle capsules 35 mg achieved an early time to maximum concentration, a similar maximum concentration, and lower systemic drug exposure compared with diclofenac potassium immediate-release tablets. In a Phase 2 study, diclofenac submicron particle capsules (18 and 35 mg) provided effective analgesia and were generally well-tolerated in a validated post-surgical model of mild to moderate pain. We evaluated the analgesic efficacy of diclofenac submicron particle capsules in a post-surgical model of moderate to severe pain.
Methods: This Phase 3 multi-center, double-blind study enrolled 428 patients 18-65 years of age who underwent a primary, unilateral first metatarsal bunionectomy with osteotomy and fixation under regional anesthesia. Patients experiencing a pain intensity rating of $\geq$40mm on a 100mm visual analog scale (VAS) were randomized to receive diclofenac submicron particle capsules (18 or 35mg; TID), celecoxib (400mg loading dose, then 200mg BID), or placebo. The primary endpoint was the summed pain intensity difference measured by VAS over 48 hrs (VAS SPID-48). Secondary endpoints included the VAS pain intensity difference (VAS PID) at various time points versus placebo.
Results: As presented recently for the primary endpoint (mean VAS SPID-48), diclofenac submicron particle 35mg (524; $P<0.001$) and 18mg (393; $P=0.01$) and celecoxib (391; $P=0.011$) demonstrated significant pain control compared with placebo. Some pain relief (mean VAS PID) was apparent in the diclofenac submicron particle 35mg (4.52) group at 30min in contrast to the placebo (0.12) group. Pain control increased over time for all active treatment groups. At 4h after dose administration, diclofenac submicron particle 35mg provided better pain control (VAS PID) versus placebo ($P=0.025$; **Figure**). At 5h after study entry, significant pain control was noted in the diclofenac submicron particle 35mg (9.43; $P=0.002$), 18mg (8.35; $P=0.009$), and celecoxib (6.62; $P=0.032$) treatment groups versus placebo (2.30; **Figure**).Overall, the most frequent treatment-emergent adverse events were localized post-procedural edema (32.7%, 140/428), nausea (29.7%, 127/428), headache (12.9%, 55/428), and dizziness (11.7%, 50/428).



Conclusions: Lower-dose, submicron particle diclofenac demonstrated better pain control at 48h (VAS SPID-48) with evidence of analgesia as early as 30 min after administration compared with placebo, and was generally well tolerated. These results suggest that diclofenac submicron particle capsules are a potentially promising therapeutic option for acute pain.

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MANAGEMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS BEFORE AND AFTER THE PHILIPPINE CLINICAL PRACTICE GUIDELINE FOR KNEE OSTEOARTHRITIS

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Purpose: We aim to review changes in physicians' practice on the management of osteoarthritis (OA) before and after the publication of the Philippine Rheumatology Association (PRA) Clinical Practice Guidelines (CPG) for knee OA in year 2010. Major highlights of the CPG were advocacy of paracetamol as first-line pharmacologic therapy followed by tramadol, good evidence for usage of glucosamine sulfate, limitation of NSAIDs usage, and emphasis on rehabilitation and lifestyle modification/advice.
Methods: This study reviewed clinical charts of patients diagnosed with primary OA (American College of Rheumatology criteria) in the Philippine General Hospital Arthritis Clinic from January to December 2009 and January to December 2011. Data regarding conventional management (non-pharmacologic and pharmacologic) and complementary/alternative therapies on the first visit were extracted. Continuous data were described using means and standard deviations while nominal data were described using frequencies and percentages. T-test for two proportions were used to compare use of different pharmacologic and alternative treatment pre- and post- CPG. P-value less than 0.05 were considered significant.
Results: One hundred eleven patients were included in the study (60 from 2009 and 51 from 2011). Mean age of symptom presentation and diagnosis were 59.7 years (SD: 10.3 years) 63.2 years (SD: 9.9 years), respectively. Majority (81.08%) were females. Mean BMI was 26.5 kg/m2 (SD: 5.03), considered obese stage I. The most common presentation was knee pain (69.8%), majority (76.48%) of which were bilateral. There were no significant differences (p-value 0.723) between the mean age between pre- (mean 59.3 years; SD 1.5 years) and post-CPG patients (mean 60.1 years; SD 1.3 years). Likewise, there were no significant differences in sex (p-value 0.2529) and proportion of dyspeptics (p-value 0.4760). Mean BMI is higher among pre-CPG patients (mean 27.9; SD 0.78) compared to post-CPG (mean 25.69; SD 0.56) and the result is statistically significant (p-value 0.03). There were statistically more patients post-CPG who had Kellgren Lawrence score of 2 compared to pre-CPG patients. The two populations had no significant difference across the rest of the scores. The use of paracetamol is significantly higher among post-CPG patients (54/60, 90% vs pre-CPG 33/51, 64.71%; p-value 0.0013) but the use of tramadol before and after CPG publication is not statistically significant (p-value 0.1119). Use of NSAID (COX-1 inhibitor) and COX-2 inhibitors was significantly lower after the CPG publication [(5/60, 8.33% vs pre-CPG 17/51, 33.33%; p-value 0.013) and (6/60, 10.17% vs pre-CPG 25/51, 49.02%; p-value 0.000), respectively]. Glucosamine sulfate use was slightly higher post-CPG (31/51, 51.67%) compared to pre-CPG (25/60, 49.02%) but this difference was not statistically significant (p-value 0.7810). Use of non-pharmacologic interventions was significantly higher post-CPG (49/60, 81.67% compared to pre-CPG 12/51, 23.53%, p value 0.0000).
Conclusion: The published CPG by the PRA significantly changed the physicians' management of patients with OA. Whether it has impacted the patients' symptoms, quality of life and overall satisfaction, however, remains to be determined and can be the subject of studies in the near future.

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A SINGLE INTRA-ARTICULAR INJECTION WITH IL-4 PLUS IL-10 AMELIORATES BLOOD-INDUCED CARTILAGE DEGENERATION IN HAEMOPHILIC MICE

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Purpose: Exposure of joint cartilage to blood can occur after joint trauma, during or after major joint surgery, or due to hemophilia. This ultimately leads to joint damage, both by direct effects of blood on cartilage and via synovial inflammation (Lafeber et al., Haemophilia 2008). The cytokines interleukine (IL)-4 and IL-10 are known as modulatory cytokines. A combination of IL-4 plus IL-10 protects against blood-induced cartilage damage *in vitro* (van Meegeren et al., Osteoarthritis & Cartilage 2012). It has been hypothesized that the combination